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Angela D'ascola
University of Messina, Policlinico Universitario
Adele Bottaro
University of Messina
Letteria Minutoli
University of Messina, Policlinico Universitario
Fabio Stagno
University of Messina
Manlio Fazio
University of Messina
Federica Aliquò
University of Messina, Policlinico Universitario
Stefania Stella
A.O.U. Policlinico "G. Rodolico-S. Marco"
Herbert Ryan Marini
University of Messina, Policlinico Universitario
Alessandro Allegra
aallegra@unime.it

University of Messina

Research Article

Keywords: astrocytes, Imatinib, IL-1, neuroprotection, chemobrain, Neuroinflammatory Disorders

Posted Date: November 20th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10826261/v1

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Additional Declarations: No competing interests reported.

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Angela D'ascola[1], Adele Bottaro[2], Letteria Minutoli[1], Fabio Stagno[2], Manlio Fazio[2], Federica Aliquò[1], Stefania Stella[3], Herbert Ryan Marini[1], Alessandro Allegra[2]

[1] Department of Clinical and Experimental Medicine, University of Messina, Policlinico Universitario, Via Consolare Valeria 1, 98125 Messina, Italy. angela.dascola@unime.it; letteria.minutoli@unime.it; federica.aliquo@unime.it; herbertryan.marini@unime.it

[2] Hematology Unit, Department of Human Pathology in Adulthood and Childhood "Gaetano Barresi", University of Messina, Via Consolare Valeria, 98125 Messina, Italy. adelebottarp15@gmail.com; fabio.stagno@unime.it; manlio.fazio@polime.it; aallegra@unime.it.

[3] Center of Experimental Oncology and Hematology, A.O.U. Policlinico "G. Rodolico-S. Marco", 95123 Catania, Italy; Department of Clinical and Experimental Medicine, University of Catania, 95123 Catania, Italy. stefania.stella@unict.it

Correspondence: Prof. Alessandro Allegra aallegra@unime.it (0000-0001-6156-8239)

Words: 5987

Statements and Declarations:

Competing Interests and Funding: None

Acknowledgments: None

All authors contributed to the study conception and design. Conceptualization: Alessandro Allegra and Angela D'Ascola; Methodology: Letteria Minutoli, Fabio Stagno, Adele Bottaro, Manlio Fazio, Stefania Stella, and Herbert Ryan Marini; Formal analysis and investigation: Angela D'Ascola and Federica Aliquò; Writing - original draft preparation: Alessandro Allegra and Angela D'Ascola; Supervision: Alessandro Allegra and Angela D'Ascola. The first draft of the manuscript was written by Alessandro Allegra and Angela D'Ascola and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Abstract

Astrocytes play a central role in the initiation and propagation of neuroinflammatory responses involved in neurodegenerative disorders, ischemic brain injury, and cancer therapy-related cognitive impairment. Increasing evidence suggests that tyrosine kinase inhibitors (TKIs) targeting BCR-ABL/PDGFR pathway , originally developed for chronic myeloid leukemia, may exert neuroprotective effects through modulation of inflammatory signaling pathways. However, the direct effects of Imatinib on activated astrocytes remain poorly characterized.

In our study, human astrocytes were stimulated with IL-1β and treated with increasing concentrations of Imatinib. After 24 h, mRNA and protein levels of the inflammatory mediators IL-6, CCL2, CXCL10, MMP-9 were assayed by qPCR and ELISA. The activation of NF-κB and p38 MAPK signaling pathways were also evaluated by using ELISA and western blot, respectively. Cell viability was determined by MTT assay.

IL-1β induced a marked inflammatory phenotype characterized by increased secretion of IL-6, CCL2, CXCL10, and MMP-9 together with activation of NF-κB and p38 MAPK pathways. Imatinib significantly attenuated these responses in a dose-dependent manner without impairing cell viability. Treatment reduced inflammatory mediator production and suppressed both NF-κB and p38 MAPK activation. These findings indicate that Imatinib directly modulates astrocyte inflammatory responses.

Imatinib exerts potent anti-inflammatory effects in activated astrocytes. These anti-inflammatory effects were associated with reduced NF-κB and p38 MAPK activation. These findings support the growing evidence that BCR-ABL/PDGFR-targeting TKIs may have therapeutic value beyond hematological malignancies and could represent promising candidates for the treatment of neuroinflammatory and neurodegenerative disorders.
Keywords: astrocytes; Imatinib; IL-1; neuroprotection; chemobrain; Neuroinflammatory Disorders.

1.0 Introduction

Neuroinflammation is increasingly recognized as a major pathogenic mechanism underlying numerous neurological disorders, including Alzheimer's disease, Parkinson's disease, ischemic brain injury, amyotrophic lateral sclerosis, and chemotherapy-induced cognitive impairment (Kempuraj et al. 2016; Perez-Gonzalez et al. 2023). Persistent activation of resident glial cells leads to the production of inflammatory cytokines, chemokines, reactive oxygen species (ROS), and matrix-remodeling enzymes, ultimately contributing to neuronal dysfunction and neurodegeneration (Hong et al. 2016).
Among glial populations, astrocytes represent key regulators of central nervous system (CNS) homeostasis. Beyond their traditional supportive functions, astrocytes actively participate in neuroimmune responses, maintenance of blood-brain barrier integrity, regulation of synaptic transmission, and neuronal survival (Qian et al 2023; Sofroniew and Vinters 2010).
Upon stimulation by inflammatory signals such as interleukin-1β (IL-1β), astrocytes undergo phenotypic and functional changes characterized by enhanced secretion of pro-inflammatory mediators including IL-6, tumor necrosis factor-α (TNF-α), C-C Motif Chemokine Ligand 2 (CCL2), C-X-C Motif Chemokine Ligand 10 (CXCL10), and matrix metalloproteinases (MMP). Persistent astrocyte activation may therefore amplify neuroinflammation and contribute to disease progression (Sharma et al. 2007; Choi et al. 2014).
Several intracellular pathways orchestrate astrocyte inflammatory activation. Among these, Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and p38 mitogen-activated protein kinase (MAPK) signaling have emerged as pivotal regulators of cytokine production and inflammatory gene transcription [Lo et al. 2014; Saha et al. 2007). Activation of these pathways promotes the expression of multiple mediators implicated in neuronal injury, blood-brain barrier disruption, and cognitive dysfunction. Furthermore, accumulating evidence indicates a close interaction between oxidative stress, c-Abl activation, inflammasome signaling, and p38 MAPK phosphorylation (Lo et al. 2014; Giovannoni and Quintana 2020).
The Abelson tyrosine kinases ABL1 and ABL2 are broadly expressed in the CNS and regulate several fundamental cellular functions, including differentiation, survival, stress responses, cytoskeletal organization, and synaptic plasticity (Schlatterer et al. 2011; Brahmachari et al. 2017). Dysregulated c-Abl activity has been implicated in Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders. Experimental studies have shown that activation of c-Abl may promote neuronal injury through modulation of oxidative stress responses, apoptotic pathways, p38 MAPK activation, and inflammatory signaling cascades (Wu et al. 2016; Marin et al. 2022).
Tyrosine kinase inhibitors (TKIs), initially developed for the treatment of chronic myeloid leukemia (Hochhaus et al. 2026), have recently attracted considerable attention as potential neuroprotective agents. Imatinib, nilotinib, dasatinib, and bosutinib have demonstrated anti-inflammatory and neuroprotective properties in several experimental models (Brahmachari et al. 2017; Srivastava et al. 2024). These effects include reduction of microglial activation, suppression of inflammatory cytokines, attenuation of blood-brain barrier disruption, modulation of oxidative stress, and improvement of cognitive performance (Lonskaya et al. 2013). Nevertheless, conflicting results have also been reported, indicating that TKI effects may be highly dependent on the specific agent, concentration, target cell population, and disease context (Srivastava et al. 2024; Abdel Aziz et al. 2016).
Among available TKIs, Imatinib has shown particular promise. Experimental studies demonstrated beneficial effects in models of cerebral ischemia, blood-spinal cord barrier disruption, and neurodegenerative disorders. Proposed mechanisms include inhibition of PDGFR-dependent signaling, reduction of inflammatory cytokine production, suppression of p38 MAPK activation, and modulation of stress-response pathways

(Adzemovic et al. 2013; Wahlgren et al. 2017; Protzmann et al. 2025; Park et al. 2025). However, the direct impact of Imatinib on inflammatory activation of astrocytes remains incompletely understood.
The present study investigated the effects of Imatinib on IL-1β-stimulated astrocytes. We specifically evaluated the modulation of inflammatory mediator production and the involvement of NF-κB and p38 MAPK signaling pathways. Our findings provide novel insights into the potential neuroprotective role of Imatinib and further support the therapeutic repurposing of TKIs in neuroinflammatory diseases.

2.0 Materials and methods

Cell culture

Immortalized astrocytes (Innoprot, Spain) were cultured in 75-cm^2 plastic flasks containing Astrocyte medium with 2% FBS, Astrocyte supplements, and penicillin/streptomycin (100 U/ml, 100 mg/ml) (Innoprot, Spain), and incubated at 37°C in humidified air with 5% CO2. At confluence, astrocytes were trypsinized, subdivided, and replated. In the present experiments, astrocytes from passage 4 to 7 were used.

Cell treatment

Cells were seeded in six-well plates ($2{,}5x10^5$cells/well), to be confluent to about 85% after 24 h. Then, cell medium was replaced with fresh medium, and cells were treated with IL-1β (Prepotech,) before the addition of Imatinib at different concentrations (1.25, 2.5, 5, 10, 20, and 30 μM). Finally, the astrocytes and medium were collected for biochemical evaluation 24 h after the last treatment.

MTT assay

Evaluation of cell viability was carried out by a colorimetric assay that measure cell metabolic activity through the reduction reaction of the 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT). Briefly, MTT was dissolved in PBS (phosphate buffer solution) to produce a yellowish solution (5 mg/ml), that was added to cultured cells 24 h after incubation with Imatinib w/o IL-1β. The mitochondrial dehydrogenases of living cells convert MTT into water insoluble MTT-formazan of dark blue color. After 2 h at 37°C, formazan crystals are dissolved with DMSO and absorbance was measured at 550 nm using a spectrophotometer (Biospectrometer basic, Eppendorf, USA). The viability was expressed as absorbance relative to control cells (% of untreated controls, considered 100%).

RNA isolation, cDNA Synthesis, and qPCR

Total RNA was extracted from the samples using Trizol reagent (Invitrogen, Carlsbad, CA, USA) and retro-transcripted using a High Capacity cDNA Synthesis Archive kit (Applied Biosystems, San Diego, CA, USA) following the manufacturer's protocols. qPCR reactions were performed in order to evaluate gene expression of CCL2, CXCL10, IL-6, MMP-9 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) by means of ready-to-use assays (Assays on demand, Applied Biosystems, San Diego, CA, USA). Reactions were carried out by using a Taqman PCR master mix (Applied Biosystems, CA, USA) and a Real Time PCR system model 7500 (Applied Biosystems, San Diego, CA, USA). After normalization against GAPDH, used as endogenous

control, the mean value of untreated astrocyte target levels was chosen as the calibrator and the results were expressed according to the $2^{-\Delta\Delta Ct}$ calculation, as fold change relative to normal controls.

Protein extraction and Western blot assay

In order to evaluate the activation of p38 MAPK , we quantified the phosphorylated form of the protein by western blot. Cells were washed twice in ice-cold PBS and the proteins were extracted by using RIPA buffer with 1nM PMSF, protease inhibitor cocktail, and phosphate inhibitor cocktail (Sigma-Aldrich, Milan, Italy). Aliquots of the protein (10µg) were mixed to Laemmli buffer (Biorad, USA) with β-mercaptoethanol and separated on a mini gel (10-12%). Then the proteins were transfered from the gel to PVDF membranes (Amersham, Little Chalfont Buckinghamshire, UK) by electroblotting. The blots were blocked in 2% bovine serum albumin, TBS, 0.1% Tween-20, for 1 h and were then incubated with specific diluted (1µg/ml) rabbit polyclonal phospho-p38 MAPK (Cell Signalling, USA) or (0.5 µg/ml) mouse polyclonal actin (Cell Signalling, USA), in 2% bovine serum albumin, TBS, 0.1% Tween 20, in a roller bottle at 4°C overnight. The membranes were washed three times with TBS, 0,1% Tween20 and then incubated with the diluted (1:5000) secondary goat anti-rabbit antibody (Cell Signalling, USA) in TBS, 0,15% Tween-20, buffer 1 h at room temperature. The blots were then washed five times in TBS/Tween-20 and the proteins were made visible using enhanced chemiluminescience (ECL; Amersham, Little Chalfont Buckinghamshire, UK). Protein band density quantification was calculated using Odissey software and comparing β-actin protein as an endogenous control to allow the normalization of phospho-p38 MAPK protein.

NF-kB p65 Transcription Factor Assay Kit

NF-kB activation was assayed by a commercial kit (Abcam, USA) consisting in the evaluation of NF-kB p50/65 subunits DNA binding activity on nuclear extracts. Briefly, astrocytes were lysed by Nuclear Extraction Kit (Abnova, USA) following manufacturer's protocol. A specific DNA oligonucleotide was added to nuclear extracts before the addiction of a specific primary antibody able to detect the bound NF-kB transcription factor subunits. After incubation with a secondary antibody, a specific reactive substrate was added for colorimetric detection at λ 450 nm. Values are expressed as relative optical density (OD) per mg of protein.

CCL2, IL-6 and CXCL10 ELISA kits

Culture cell medium was centrifuged at 3000 rpm for 5 min in presence of 1nM PMSF and protease inhibitor cocktail. The supernatants were assayed for CCl2, IL-6 and CXCL10 determination by using specific commercial ELISA kits (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's protocol.

Protein determination

The amount of total protein was determined using Coomassie Plus-Bradford Assay™ Kit (Bio-Rad Lab., Berkeley, CA, USA) using bovine serum albumin as a standard, in accordance with the manufacturer's protocol.

Statistical analysis

All data were analysed by one way analysis of variance (ANOVA) followed by the Tukey's post-test. The statistical significance of differences was set at $P < 0.05$. Data are expressed as the mean ± S.D. values of at least five experiments for RT-qPCR and ELISA and three for western blot.

During manuscript preparation, Microsoft 365 Copilot (GPT-5 chat model) was used solely as an auxiliary tool for language refinement, figure conceptualization, and organizational support. All scientific content was independently produced, reviewed, and approved by the authors.

3.0 Results

Effect of Imatinib on cell viability

To assess the effect of Imatinib on astrocytes viability and choose the concentrations for the treatments, we performed a dose-response experiment, adding Imatinib at doses: 1.25, 2.5, 5, 10, 20, and 30 μM. In other plates, Imatinib was added in combination with 5ng/ml IL-1β to verify the possible toxic effect of the co-treatment. As reported in Fig.1 panel A, Imatinib reduced cell viability at concentrations higher than 5 μM. Based on our finding, these doses were considered toxic and excluded in all subsequent experiments.

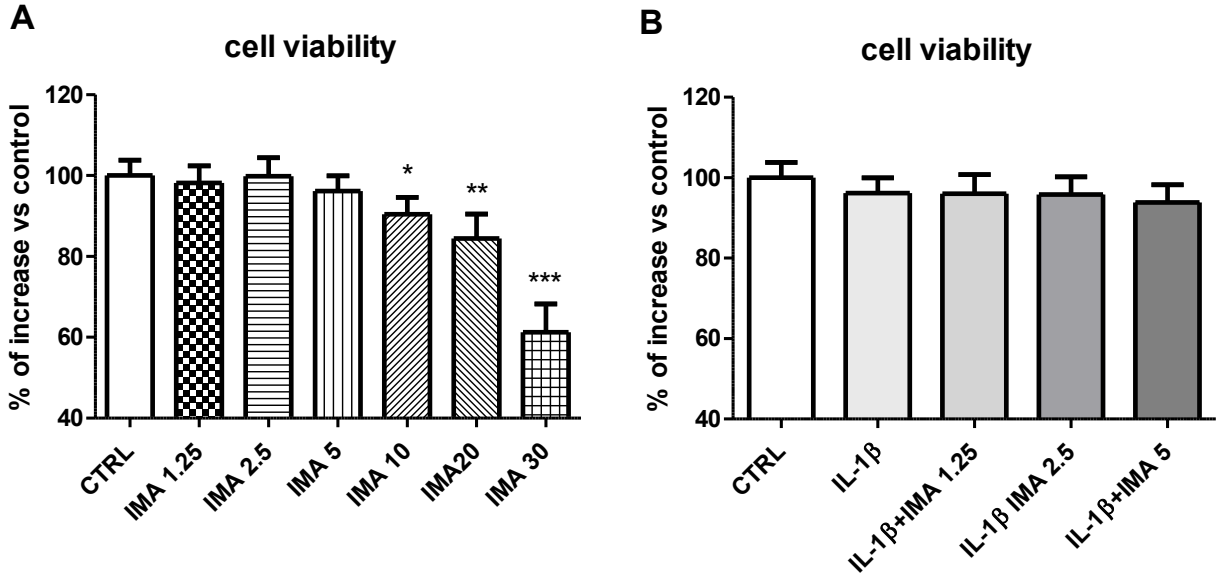


Fig.1 Dose-response effect of Imatinib on astrocytes viability (panel A). Effect of Imatinib on astrocytes stimulated with IL-1β (panel B). Values are the mean ± S.D. of no less than five experiments and are expressed as the % increase with respect to controls. *p<0.05, **p<0.01, and ***p<0.001 vs CTRL.

The stimulation with 5 ng/ml IL-1β induced only a slight and not significative reduction in cell viability (Fig.1, panel B). Notably, the addition of Imatinib did not exert any effect, indicating that these doses did not impair cell viability.

Imatinib mitigated inflammatory mediator production in *IL-1β-stimulated astrocytes*

Fig.2 reports the qPCR analysis (panel A, B, C, and D) and ELISA assays (panel E, F, and G), conducted in order to evaluate the gene expression of inflammatory mediators CCL2, CXCL10, IL-6 and MMP-9 in astrocytes. Notably, Imatinib was able to reduce both mRNA and protein levels and of CCL2, CXCL10, and IL-6, in a dose-dependent manner, attenuating the stimulatory effect induced by in IL-1 -β in astrocytes. In addition, the treatment with Imatinib reduced the mRNA levels of MMP-9 .

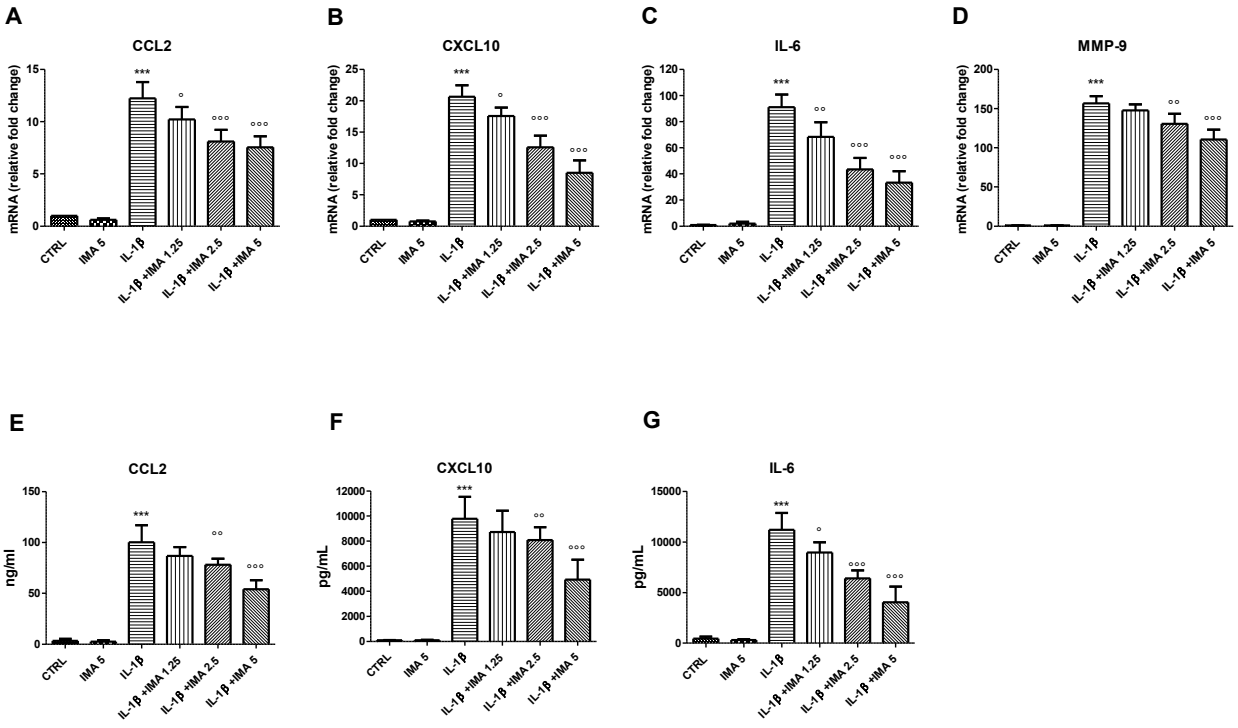


Fig. 2 Effect of Imatinib on *CCL2*, *CXCL10*, *IL-6, and MMP-9* mRNA levels (panels A, B, C, and D), and related protein production (panels E, F, and G) in astrocytes treated with IL-1 β and control cells. Values are the mean ± S.D. of no less than five experiments and are expressed as fold change with respect to controls. *** $p < 0.001$ vs. CTRL; ° $p < 0.05$, °° $p < 0.01$ and °°° $p < 0.001$ vs IL-1 β.

Imatinib reduced NF-kB activation in *IL-1β-stimulated astrocytes*

In order to evaluate the effect of Imatinib on NF-kB activation induced by IL-1β, the changes in the NF-kB p65 concentration into the nuclei of astrocytes were assayed. As shown in Fig.3, IL-1β induced a significant increase in the NF-kB activation, while pre-treatment with Imatinib reduced NF-kB activity at the highest concentrations. These results suggest that Imatinib exerts its anti-inflammatory effect partially through the

reduction of NF-κB DNA binding activity. Therefore, NF-kB activation and the consequent inflammatory response could be modulated by Imatinib.

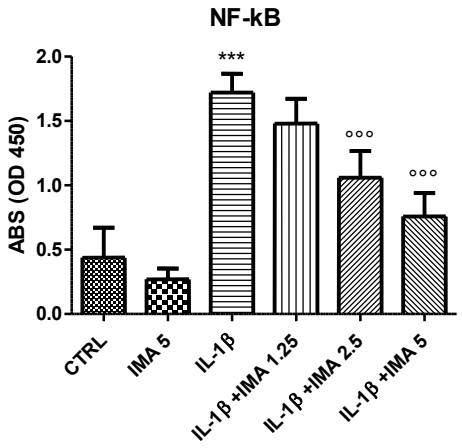


Fig. 3 Effect of Imatinib on *NF-kB activation* in astrocytes treated with IL-1 β and control cells. Values are the mean ± S.D. of no less than five experiments and are expressed as fold change with respect to controls. *** $p <$ 0.001 vs. CTRL; °°° $p < 0.001$ vs IL-1 β.

Imatinib reduced p38 MAPK activation in *IL-1β-stimulated astrocytes*

The activation of p38 MAPK was assayed in order to evaluate the involvement of this crucial mediator in inflammatory pathways. Western blot data showed that IL-1β treatment increased the protein levels of the phosphorylated protein, the active form of p38 MAPK (Fig. 4). In contrast, the treatment with Imatinib in combination with IL-1β addition reduced the response obtained with pro-infammatory cytokine alone, while no effects were observed in unstimulated cells (Fig. 4).

Together these findings indicate that the anti-inflammatory effects of Imatinib are associated with reduced activation of both p38 MAPK and NF-κB.

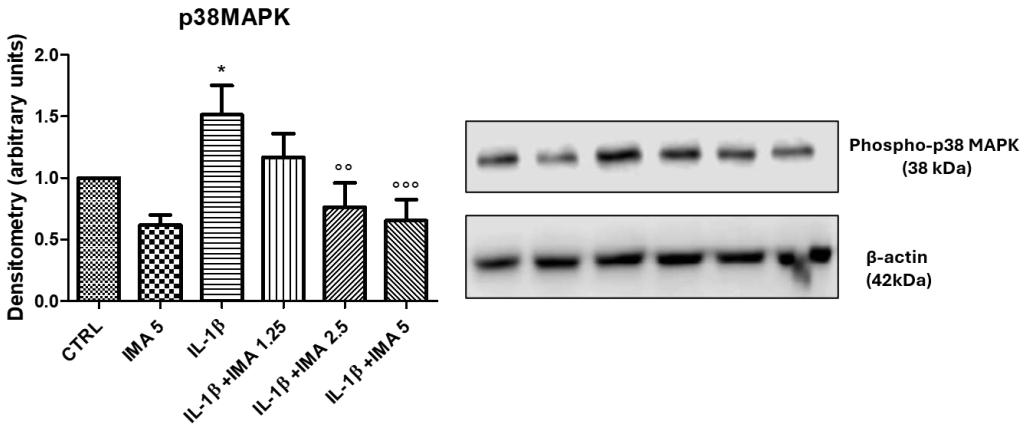


Fig. 4 Effect of Imatinib on Phospho- *p38 MAPK* protein levels in astrocytes treated with IL-1 and control cells. Values are the mean ± S.D. of three experiments and are expressed as fold change with respect to controls. * $p < 0.05$ vs. CTRL; °° $p < 0.01$ and °°° $p < 0.001$ vs IL-1b.

4.0 Discussion

The present study demonstrates that Imatinib significantly attenuates IL-1β-induced astrocyte activation and that these effects are associated with reduced NF-κB and p38 MAPK activation, leading to reduced production of the inflammatory mediators IL-6, CCL2, CXCL10, and MMP-9. These findings provide novel evidence that astrocytes represent a direct cellular target of Imatinib and support the growing concept that tyrosine kinase inhibitors may exert clinically relevant neuroprotective effects independent of their antineoplastic activity.

Although most previous investigations have focused on neurons or microglia, increasing evidence indicates that astrocytes play a pivotal role in both the initiation and maintenance of chronic neuroinflammation. Astrocytes are now recognized as dynamic regulators of synaptic homeostasis, metabolic support, blood-brain barrier (BBB) integrity, and neuroimmune signaling (Heithoff et al. 2021).

Under inflammatory conditions, activated astrocytes acquire a reactive phenotype characterized by increased production of cytokines, chemokines, matrix metalloproteinases, and reactive oxygen species. These mediators amplify neuroinflammation by establishing a bidirectional signaling loop with microglia, ultimately contributing to neuronal dysfunction and neurodegeneration. Consequently, suppression of astrocyte activation has emerged as an attractive therapeutic strategy for several neurological disorders (Liddelow et al. 2017; Kwon and Koh 2020; Vandenbark et al. 2021).

One of the most relevant findings of our study is the inhibition of p38 MAPK activation. The p38 pathway is considered a central regulator of neuroinflammatory responses and is activated by multiple stress signals, including IL-1β, oxidative stress, mitochondrial dysfunction, and DNA damage. Activation of p38 promotes transcription of numerous inflammatory genes and amplifies cytokine production through both transcriptional and post-transcriptional mechanisms (Han et al. 2020; Cuenda and Rousseau 2007).

Previous studies demonstrated that c-Abl signaling can directly phosphorylate and activate p38α, thereby linking oxidative stress to inflammatory and apoptotic pathways. Experimental inhibition of c-Abl by Imatinib has been shown to reduce p38 activation and protect dopaminergic neurons in models of Parkinson's disease (Brahmachari et al. 2017; Wu et al. 2016).

The reduction of p38 phosphorylation observed in our astrocyte model is consistent with modulation of this signaling pathway in glial cells, and suggests that Imatinib may interrupt a critical signaling axis involved in neuroinflammatory amplification.

Our results also indicate marked suppression of NF-κB activation. NF-κB represents one of the most important transcription factors controlling inflammatory responses in the central nervous system. Following activation, NF-κB induces expression of cytokines, chemokines, adhesion molecules, and matrix-degrading enzymes that contribute to tissue injury and recruitment of additional inflammatory cells (Liu et al. 2017; Anilkumar and Wright-Jin 2024).

Notably, crosstalk between p38 MAPK and NF-κB signaling has been described in both astrocytes and microglia, creating a self-sustaining inflammatory network (Saha et al. 2007). The observed reduction in both NF-κB and p38 MAPK activation suggests that Imatinib may influence multiple inflammatory signaling programs upstream of inflammatory mediator production, rather than targeting a single mediator. This broad anti-inflammatory effect may explain the significant reductions observed in IL-6, CCL2, CXCL10, and MMP-9 (Liu et al. 2017; Arthur and Ley 2013).

The reduction of IL-6 deserves particular attention because this cytokine is increasingly considered a critical mediator linking systemic inflammation to cognitive dysfunction. Elevated IL-6 levels have been reported in Alzheimer's disease, Parkinson's disease, stroke, and chemotherapy-associated cognitive impairment (Shan et al. 2024; Quillen et al. 2023; Pawluk et al. 2025; Cheung et al. 2015).

Experimental evidence indicates that IL-6 contributes to synaptic dysfunction, neurovascular alterations, and impaired hippocampal plasticity. Therefore, suppression of IL-6 production by Imatinib may have implications extending beyond simple control of neuroinflammation and could potentially affect cognitive outcomes (Nelson et al. 2012; Stephenson et al. 2024).
Similarly, the reductions in CCL2 and CXCL10 may be highly relevant from a translational perspective. Both chemokines play major roles in leukocyte recruitment, activation of resident glial populations, and propagation of chronic neuroinflammatory responses (Babcock et al. 2003).
Increased expression of CCL2 and CXCL10 has been associated with BBB dysfunction, neurodegeneration, and cognitive decline. Their downregulation by Imatinib suggests that the drug could interfere with the establishment of a sustained inflammatory microenvironment within the CNS (Semple et al. 2010; Kiyota et al. 2013).
Another particularly interesting observation was the decrease in MMP-9 expression. Matrix metalloproteinase-9 is involved in extracellular matrix degradation, BBB disruption, and neurovascular injury. Increased MMP-9 activity has been documented in several neurodegenerative and neuroinflammatory conditions and is associated with enhanced infiltration of inflammatory cells into the CNS (Barr et al. 2010; Turner and Sharp 2016).
Importantly, previous studies demonstrated that Imatinib preserves blood-spinal cord barrier and BBB integrity through modulation of PDGFR-dependent pathways. Consequently, inhibition of MMP-9 may represent a complementary mechanism through which Imatinib protects the neurovascular unit (Adzemovic et al. 2013 ; Zhan et al. 2015).
An additional potential implication of our findings concerns chemotherapy-associated cognitive impairment (chemobrain). Neuroinflammation is increasingly recognized as an important contributor to cognitive dysfunction following cancer treatment, and activated astrocytes are believed to participate in this process. The ability of Imatinib to reduce astrocyte production of IL-6, CCL2, CXCL10, and MMP-9 suggests a mechanism that may be relevant to neuroinflammatory pathways implicated in chemobrain. However, dedicated experimental models will be required to determine whether these cellular effects translate into measurable cognitive benefits (Rao et al. 2022; Allegra et al. 2020; Bagnall-Moreau et al. 2019; Nguyen and Ehrlich 2020).
Moreover, previous studies have shown that other TKIs may improve cognitive performance and reduce neuroinflammation in experimental models. These observations raise the possibility that Imatinib could exert similar protective effects in the context of chemotherapy-induced CNS injury (Kim et al. 2022; Mohammad et al. 2024).
A further argument supporting this hypothesis derives from the involvement of astrocytes in the pathophysiology of chemobrain. Astrocytes are increasingly recognized as key mediators of treatment-related neurotoxicity because they integrate peripheral inflammatory signals and regulate neuronal metabolism, glutamate handling, antioxidant defenses, and BBB stability. By directly targeting astrocyte inflammatory activation, Imatinib may interrupt one of the earliest cellular events occurring during development of chemotherapy-associated cognitive deficits. This mechanism may be particularly relevant in hematologic malignancies, where long-term exposure to targeted therapies and systemic inflammatory stimuli frequently coexist (Lee et al. 2022; Santello et al. 2019).

4.1 Study limitations and future perspectives

Nevertheless, caution is warranted when translating these findings into clinical applications. The neurological effects of TKIs appear to be highly drug-specific and context-dependent. While numerous studies have reported neuroprotective actions of Imatinib, nilotinib, dasatinib, and bosutinib, other investigations have described cognitive impairment, oxidative stress induction, or cerebrovascular complications associated with certain TKIs. Differences in BBB penetration, target selectivity, dosage, and treatment duration may explain these apparently conflicting observations (Mulder 2014; Sasaki 2025). Therefore, future studies should carefully define the therapeutic window required to maximize neuroprotective benefits while minimizing potential adverse effects.

Furthermore, other limitations should be acknowledged. First, our findings were obtained using an in vitro experimental model of astrocytes, which cannot fully reproduce the complexity of the central nervous system microenvironment. In vivo, astrocytes continuously interact with neurons, microglia, oligodendrocytes, endothelial cells, and infiltrating immune cells, generating a network of bidirectional signals that may influence the biological effects of imatinib. Consequently, the observed responses may not completely reflect those occurring in physiological or pathological conditions within the intact brain.
In addition, the molecular mechanisms underlying the effects of imatinib were evaluated only indirectly. Although reductions in NF-κB and p38 MAPK activation were observed, the present study was not designed to establish a direct causal relationship between these signaling pathways and the anti-inflammatory effects of Imatinib.
Even though our results suggest the involvement of pathways related to inflammation, cellular activation, and stress responses, specific signaling mediators were not investigated in detail. Further studies incorporating mechanistic analyses, including the assessment of NF-κB activation, MAPK signaling, oxidative stress markers, and cytokine networks, as well as validation in animal models, will be necessary to better define the pathways responsible for the observed effects and to establish their translational relevance. Moreover, further investigations using co-culture systems, organoids, and animal models of neurodegeneration and chemobrain will be required to validate our findings. In addition, future investigations should explore the effects of Imatinib on NLRP3 inflammasome activation, oxidative stress pathways, mitochondrial homeostasis, and astrocyte-microglia crosstalk.
To our knowledge, this is among the first studies demonstrating a direct anti-inflammatory effect of Imatinib in human astrocytes challenged with IL-1β. Overall, our results are consistent with a model in which Imatinib modulates astrocyte inflammatory responses in association with reduced NF-κB and p38 MAPK signaling, resulting in reduced inflammatory mediator production and potentially improved preservation of neuronal and neurovascular homeostasis. Beyond their mechanistic relevance, these findings are of translational interest because Imatinib is a clinically established agent with well-characterized pharmacokinetics and long-term safety. Consequently, our observations support further investigation of Imatinib as a repurposed therapeutic strategy for neuroinflammatory conditions and other disorders characterized by chronic glial activation
Beyond its implications for neurodegenerative diseases, these observations strongly suggest that Imatinib deserves further investigation as a candidate strategy for limiting neuroinflammation-driven cognitive impairment associated with cancer therapy. Drug repurposing has emerged as an attractive strategy for neurological disorders, where the development of novel compounds remains associated with high costs and elevated failure rates. Repurposing clinically established agents may accelerate translation to patients because pharmacokinetic properties, safety profiles, and long-term toxicities are already well characterized. Among these agents, tyrosine kinase inhibitors represent promising candidates because of their reported anti-inflammatory and neuroprotective activities. However, the direct effects of Imatinib on activated human astrocytes remain poorly understood.

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